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Monocyte Chemoattractant Protein-1 (MCP-1), Chemokine Receptor2 Gene Polymorphism and Level of MCP-1 in Behcet's Disease: A Case-Control Study

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Abstract

Bachground: Behcet's disease (BD) is chronic autoimmune vasculitic disease, its pathogenesis still unclear, it could be a combination of environmental and genetic factors. Both MCP-1 and its receptor CCR2 have been incriminated in the pathogenesis of multiple inflammatory disorders.

Aim of Study: The aim of this study wasto investigate the potential associationof serum of monocyte chemoattractant protein-1 (MCP-1), genetic derangement of MCP-1 and chemokine receptor2 (CCR2) with Behcet's disease.

Patients and Methods: Thirty BD patients' blood samples were gathered and 30 healthy subjects with matching age and sexa, were tested for blood MCP-1 using Enzyme linked Immunosorbant assay (ELISA), MCP-1 c. 2518A/G and CCR2 -V641 polymorphism as determined by polymerase chain reaction (PCR). Assessment of disease activity was done using Behcet's Disease Current Activity Form (BDCAF).

Results: The studied patients mean age was 34.9±12.2 years, mean age of disease onset was 26.7±8.8 years and mean disease duration 6.9±7.3 years. Blood levels of MCP-1 in BD patients was 241.7±179.45mg/l versus 23.1±27.06mg/l in healthy subjects and the difference between both groups was significantly high (p<0.0001). MCP-1 was positively correlated with disease activity, but it did not reach statistically significant value (p>0.05). Level of MCP-1 was higher in subjects with heterozygous MCP-1 and CCR2 genes (310±247.74mg/l) compared to subjects with normal MCP-1 and CCR2 genes and the difference was significantly high (p<0.0001). MCP-1 gene polymorphism was positive in 30% of cases versus 16.1% in healthy controls with (p>0.05). Heterozygous CCR2 gene was positive in 9 Behcet'sdisease patients and in 5 of the control group (p>0.05).

Conclusion: MCP-1 serum level was significantly higher in BD cases in comparison to control group, in addition it was significantly high in subjects with heterozygous MCP-1 and CCR2 compared to those with normal one. This could providemore understanding of BD pathogenesis and suggest new therapeutic modalities.

Key Words: *Monocyte chemoattractant protein-1 – Chemokine receptor2 – Behcet's disease.*

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Introduction

BEHÇET'S disease (BD) is a systemic autoimmune vasulitic disease of unknown etiology, characterized by recurrent inflammatory episodes with random duration and frequency from the start and a unique geographic distribution. Being a systemic vasculitic disease, everyarea in the body with high vascularization can be affected [1].

The Turkish dermatologist Hulusi Behçet first described this disease in 1937 as a triad that associates uveitis with oral and genital ulcers. Since that time, other signs have been described and updated including new aspects of epidemiology, pathogenesis and management [2].

The etiopathogenesis of BD is still unclear. The condition is possibly multifactorial resulting from a combination of genetic and environmental factors ignited by exacerbated cytokine production and immune dysfunction. However, a particular variation in the HLA-B gene has been associated with the predisposition for BD [3]. It is reported that carriage of the HLA-B51 allele in different ethnic group sincreases the risk of developing BD by about a factor of six [4]. Other genes within the HLA region such as A*26 and Cw* 1602 were also reported to be linked with BD [5]. Apart from HLA susceptibility genes, Genome-wide association

studies (GWAS) have described increasedgenetic risk for BD with common variants within the IL-10 [6].

Monocyte chemoattractant protein- 1(MCP-1), also known as Chemokine (CC-motif) ligand 2 (CCL2) or small inducible cytokine A2, is a member of the CC chemokines superfamily. It plays a crucial role in the inflammatory processby recruiting many inflammatory cells such as macrophage/ monocytes, memory T cells and dendritic cells in addition to cytokines leading to multiple disorders [7].

The MCP-1 receptor, called C-C motif chemokine receptor type 2 (CCR2) can be expressed by both hematopoietic cells such as macrophages and non-hematopoietic cells such as endothelial cells, fibroblasts, and mesenchymal stem cells. It has both pro-inflammatory effects mostly mediated by antigen presenting cells (APCs) and T cells, and some anti-inflammatory actions served mainly by regulatory T cells effects [8].

Both MCP-1 and its receptor CCR2 have been incriminated in the pathogenesis of many diseases-such as corona virus infections, cancers, neuroinflammatory disorders, rheumatoid arthritis, neuroinflammatory and cardiovascular disorders [9]. Elevated serum MCP-1 levels have also been previously detected in patients with active BD [10].

The aim of current study was to assess level of serum MCP-1, genetic derangements of MCP-1 and CCR2 and the susceptibility to BD in Egyptian patients.

Patients and Methods

Subjects:

This study was conducted between 2018-2019, sixty subjects were enrolled: 30 patients completing the international study group diagnostic criteria for Behcet's disease [11], recruited from Rheumatology Inpatient Department, Kasr Alaini university hospital including 4 females in addition to 26 male patients who were between the ages of 17 and 73. Their symptoms began between the ages of 6 and 47 and range of disease duration was between 1 and 35 years. Patients with active infection, malignancies, or coexistent inflammatory or autoimmune disease were excluded from the study. Every patient underwent a history taking, physical examination, and lab tests. The Behcet's Disease Current Activity Form was used to assess current disease activity (BDCAF) [12]. In addition, this work included 30 healthy individuals as control group who their sex and agematched to the cases.

Sample collection:

Under aseptic conditions Every participant had their venous blood (3ml) drawn into sterilized ethylene diamine tetra acetic acid (EDTA) vacutainer tubes, which were processed shortly after sampling.

Serum MCP1 determination: Quantitative sandwich enzyme-linked immunosorbent assay (Human CCL2 (MCP-1) ELISA kit, Bioscience, Inc) was used to determine level of serum MCP-1 following the directions provided by the manufacturer.

Determination of MCP-1 c.2518A/G genotype:

From each patient's EDTA-treated whole blood, peripheral leukocytes were separated, and genomic DNA was taken for MCP-1 polymerase chain reaction (PCR) amplification. (Sigma- Thermo Scientific DNA polymerase) was used for DNA extraction, PCR reactions were done using ready to use master mix (Sigma Fast Start SYBR Green Master). For amplificationthese primers were utilized: forward 5'-The absorbance (OD) was measured at 450nm by an ELISA plate reader. MCP-1 concentration was estimated using a reference standard calibration curve.

CCGAGATGTTCCCAGCACAG-3' and reverse 5'-CTGCTTTGCTTGTGCCTCTT-3'. After that, the tubes were added to the thermal cycler (Perkin Elmer 9600, Singapore). Following was the PCR cycle program: Cycling at 94° for one minled to the DNA's amplification, 55° for one min, and 72° for one min and thirty seconds. After forty cycles, the response was prolonged for anotherten minutes at 72°. Following PCR amplification, the PCR result underwent nighttime constraint digestion at 37° with PvuII (5U) according to the method described by [13], Agarose gel electrophoresis of the digested products was carried out. They were analyzed using ultraviolet light after staining with ethidium bromide to identify the existence of the different genotypes: (1) Only one 930bp band is produced by the A/A genotype; (2) Two bands (222bp and 708) are produced by the G/G genotype; and (3) Three bands are produced by the A/G genotype (222bp, 708bp and 930bp).

Determination of the CCR2-V64I polymorphism:

Polymerase chain reaction (PCR) was used to determine the CCR2-V641 polymorphism by sequence-specific primers (SSP) proceeded by agarose gel electrophoresis. 2 PCR reactions were done for all samples by a reverse primer and two separate forward primers (CCR2-64V and CCR2-64I). Amplification of Genomic DNA (130ng) was

done in a (ten-µl) reaction mixture which contain-sten picomoles of each CCR2-V64I primers: F (CCR2-64V), 5'TGGGCAACATGCTGGTCG3' or F(CCR2-64I), 5'TGGGCAACATGCTGGTCA3' and R, 5'TGGAAAATAAGGGCCACAGAC3' and 5-µl 2 x Immo MixTM (Bioline). DNA extraction was done using (Sigma-Thermo Scientific DNA polymerase). PCR reactions were done usingmaster mix (Sigma Fast Start SYBR Green Master).In the thermal cycler (Perkin Elmer 9600, Singapore) the tubes were then placed. Following is the PCR cycle program: A denaturing step was initiated at (95°C) for two minutes and thirty seconds. Ten higher-stringency cycles of denaturing at 94°C for twenty-five s, annealing at (60°C) for forty-five s and extending at (72°C) for forty-five s again proceeded by 21 lower-stringency cycles of denaturing at 94°C for twenty-five s, annealing at (58°C) for forty s and extending at (72°C) for forty s finally extending at (72°C) for six minutes. The PCR reaction parameters were adjusted and altered as described by **[14]**.

The 413-base pair (bp) amplified PCR products were processed on a agarose gel with 1.5% and stained with ethidium bromide using an O' Gene RulerTM 50bp DNA Ladder, which is ready to use (Thermo-Fisher scientific Inc, Mass achusetts, USA). PCR was amplified by the samples using the CCR2-64V forward primer but did not produce any products using the CCR2-64I forward primer because individuals have the CCR2 gene's wild-type allele (G) at location 190. The CCR2-64V forward primer did not produce any product in samples having a mutant allele (A) at site 190 of the CCR2 gene; however, the CCR2-64I forward primer amplified the samples instead. The samples that were heterozygous for CCR2-64V and CCR2-64I forward primers both produced PCR results.

Statistical analysis:

Statistical Package for the Social Sciences (SPSS) version 20.0 statistical software was utilised for the study of statistics. Data were presented as mean, standard deviation, median, and minimum and maximum values. Independent sample *t*-test was performed to identify significant group differences for normally distributed data. The Pearson method was used to determine correlations between normally distributed parameters. A 0.05 or less *p*-value was significant.

Results

In this study sixty subjects were recruited: 30 subjects diagnosed clinically with Behcet's disease including 4 female (13.3%) and 26 (86.7%) male patients with mean age of 34.9±12.2 years (17-73 years) and disease duration of 6.9±7.3 years (1-35 years) and age of onset 26.7±8.8 years (6-47 years), in addition to 30 age and sex matched healthy controls.

Active clinical manifestationsof patients during the study were oral ulcers (23.3%), genital ulcers (6.7%). Skin pustules was observed in 16.7% of cases and erythema nodosum was found in 6.7% of patients. Active ocular involvement in 20% of cases, arthralgia was presented by 16.7% of cases and arthritis in 3.3% of cases recruitedin this study. headache was found in 23.3% of cases. The mean total activity score of BD patients was1.3±1.5 (0-5). All patients received steroids with mean daily dose 16.2±8.7mg/d. The different clinical parameters, laboratory findings and treatment received by BD cases are represented in Table (1).

Table (1): Clinical parameters, laboratory findings and treatment received by Behcet's disease patients.

Parameter n (%) or mean ± SD	BD patients (n=30)
Oral ulcer	7 (23.3)
Genital ulcer	2 (6.7)
New ocular involvement	6 (20)
Skin pustules	
Superficial vein Thrombosis	5 (16.7)
Erythema nodosum	3 (10)
New major vessel involvement	2 (6.7)
Arthralgia	2 (6.7)
Arthritis	5 (16.7)
New nervous system involvement	1 (3.3)
Headache	1 (3.3)
BDCAF	7 (23.3)
Total Activity Score	1.3±1.5
ESR (mm/1 st h)	18±8.4
Steroid Dose (mg/d)	16.2±8.7
Azathioprin	9 (30)
Cyclosporin	8 (26.7)
Cyclophosphamide	5 (16.7)
Methotrexate	2 (6.7)
Infliximab	5 (16.7)
Mycophenolate mofetil	1 (3.3)

BD: Behcet disease. ESR: Erythrocyte Sedimentation Rate.

Serum level of MCP-1 was significantly higher in Behcet's disease patients compared to controls (p<0.0001), as shown in Table (2).

Table (2): Comparison between Behcet disease (BD) patients and control as regardsblood levels of MCP-1.

Parameter (Mean ± SD)	BD patients (n=30)	Control (n=30)	*p*-value
Blood level MCP-1 (mg/L)	241.7±179.45	23.1±27.06	<0.0001

BD: Behcet disease. MCP-1: Monocyte chemoattractant protein-1.

The cases and controls were analyzed in relation to heterozygous MCP1 and CCR2 gene polymorphisms. The percentage of cases with normal MCP 1 genes was estimated to be 70% versus 80.6% in the control (p=0.334). Additionally, heterozygous MCP1 gene polymorphisms were found in 30.0% of cases versus 16.1% of controls (p=0.198). The percentage of cases with normal CCR2 genes was noted to be 70% versus 80.6% in the control (p=0.334). Furthermore, heterozygous CCR2 gene polymorphisms were found in 30.0% of cases versus 16.1% of controls (p=0.198), as shown in Table (3).

Table (3): Comparison between Behcet disease (BD) patients and control as regards normal and heterozygous MCP1 and CCR2 genes.

Parameter n (%)	BD patients (n=30)	Control (n=30)	p-value
MCP1 n	21 (70.0)	25 (80.6)	0.334
MCP1 hetero	9 (30.0)	5 (16.1)	0.198
CCR2 n	21 (70.0)	25 (80.6)	0.334
CCR2 hetero	9 (30.0)	5 (16.1)	0.198

BD : Behcet disease.
MCP-1 : Monocyte chemoattractant protein-1.
CCR2 : Chemokine receptor2.
N : Normal.
Hetero : Heterozygous.

Blood levels of MCP1 correlated positively with age, age of disease onset, duration of the disease, ESR, steroid doses used and total activity scores, but without statistical significance, as shown in Table (4).

Table (4): The correlation between blood MCP1 levels and various parameters in BD patients.

Parameter r (p)	MCP-1 (mg/L)
Age	0.103 (0.588)
Age of onset	0.049 (0.796)
Disease duration	0.036 (0.85)
ESR (mm/1 st h)	0.237 (0.207)
Steroid dose	0.161 (0.396)
Total activity score	0.301 (0.106)

MCP-1: Monocyte chemoattractant protein-1.

The blood levels of MCP1 were higher in participants with heterozygous MCP1 genes (310.8± 247.74) mg/l compared to subjects with normal MCP1 genes (78.1±80.67) mg/l and the difference was found to be highly significant (p<0.0001). Similarly, the blood levels of MCP1 were higher in participants with heterozygous CCR2 genes compared to subjects with normal CCR2 genes and the difference was found to be significantly high (p<0.0001), (Table 5).

Discussion

BD is chronic autoimmune rheumatic disease characterized by recurrent attacks of acute inflammation [15]. Patients with BD present with wide spectrum of manifestations including mucocutaneous lesions, uveitis, arthritis, neurological, cardiovascularand gastrointestinal manifestations [16].

Pathogenesis of BD still not fully understood it could be related to disturbance of innate and adaptive immunity with genetic background [17].

The monocyte chemoattractant protein 1 (MCP1) is a cytokine that regulates monocyte/ macrophage chemotaxis together with its receptor CCR2 are involved in the pathogenesis of various diseases [18].

The MCP1 gene polymorphism has been associated with various inflammatory disorders including lupus nephritis and rheumatoid arthritis [19]. The MCP-1 receptor, called chemokine receptor type 2 (CCR2) is expressed by cells such as macrophages, endothelial cells, fibroblasts, and mesenchymal stem cells. It has both pro-inflammatory and some anti-inflammatory effects [20].

The CCR2 gene polymorphism has been known to be associated with various inflammatory disorders [21].

The current study comprised 30 subjects diagnosed clinically with Behcet's disease (4 females and 26 males) and 30 healthy controls, aiming to investigate the potential association of serum MCP-1, MCP-1 and CCR2 gene polymorphism with Behcet's diseasepathogenesis.

The mean blood level of MCP-1 participating subjects in the current work was noticed to be significantly higher in Behcet's disease cases versus that of the controls and the difference was found to be highly significant (p<0.0001). Several studies have highlighted the association of high MCP1 and the risk of development of several inflammatory and autoimmune diseases.

A study by Harigai and his colleagues suggested the production of MCP-1 by the synovium of inflamed joints. Inrheumatoid arthritis MCP-1 and other proinflammatory cytokines were found to contribute todisease pathogenesis [22].

Another study by Cho et al., carried out onpatients with Behcet's disease found that the levels of MCP 1 were more than double the levels found in normal subjects [23].

Similarly, Ibrahim and colleaguesreported a highly significant increase in MCP1 level in a group of patients with Behcet's disease compared to the control group **[24]**, additionally Kaburaki et al., and DO et al., demonstrated high levels of MCP1 in Behcet's disease patients in comparison to healthy controls in two separate studies **[25,26]**.

On the other hand, a study by Ozer and his associates found comparable levels of MCP1 in cases and healthy controls **[27]**. This discrepancy may be due to different sample sizes obtained and variations of populations observed in the study groups.

In agreement with results of the current study, Ibrahim and colleagues found a highly significant increase in MCP1 level in a group of patients with Behcet's disease compared to the control group **[24]**, Similarly Kaburaki et al. and DO et al., demonstrated high levels of MCP1 in Behcet's disease patients in comparison to healthy controls in two separate studies **[25,26]**.

Within this research, a positive correlation was found between MCP1 level and disease activity. However, the correlation was found to be statistically insignificant. In line with these results another study found a positive correlation between MCP1 level and patients with active Behect's disease which reached a statistically significant value **[24]**. Cho et al., also found a strong positive correlation between MCP1 levels and Behcet's disease manifestations such as gastrointestinal Behcet's disease **[23]**.

In the ongoing study, the blood levels of MCP1 were found to be significantly higher whether in participants with heterozygous MCP1 genes or heterozygous CCR2 genes compared to subjects with normal MCP 1or CCR2 genes and it was determined that the difference was quite considerable. (p<0.0001).

Like that, the study by Cho and his colleagues obsereved that subjects with genetic mutations of MCP1 were found to have higher serum levels of serum MCP1 **[23]**, Another study reprted that CCR2 polymorphism was associated with high MCP1 levels in a group of patients with hepatitis C **[28]**.

The present study found that the percentage of Behcet's disease cases with normal MCP 1or CCR2 genes was estimated to be 70% versus 80.6% of the subjects participating in the control group and the difference between them was not considered to be statistically significant. Additionally, heterozygous MCP1 or CCR2 gene polymorphisms were found in 30.0% of Behcet's disease cases versus 16.1% of controls. However, the statistical significance of this discrepancy was not established.

In agreement with our results Ghaffari et al., conducted case control study on a group of Iranian patients with Bechet's disease and found no significant difference in MCP-1 gene polymorphism between patients and healthy controls **[29]**, in similar fashion a study by Ye and colleaguesreported no significant difference MCP-1 and CCR2 gene polymorphism in a group of Chinese patients with systemic lupus **[30]**, on the other hand Hou and his colleagues investigated MCP-1 gene polymorphism in a group of Chinese patients with Behcet's disease and it was significantly high **[31]**.

These conflicting results in the literature regarding association of MCP-1 gene polymorphism with Bechet's disease may be explained by genetic variations in different ethnic groups. Further studies are recommended on a larger number of patients to investigate the possibleassociation MCP-1 and CCR2 gene polymorphism with Behcet's disease.

In conclusion, our study demonstrated that serum level MCP1 was significantly higher in Behcet's disease patientsin comparison to healthy controls, also it was highly significant in subjects with heterozygous MCP-1 and CCR2 genes in comparison to those with normal MCP-1 and CCR2 genes which suggest the possible association of serum MCP-1, MCP-1 and CCR2 gene polymorphism with Behcet’s disease pathogenesis. Furthermore, anti-cytokine and gene therapy may be crucial to the course of treatment of Behcet's disease in the future. Further studies need to be conducted in this field.

Conflicts of interest: None.

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تعدد الأشكال الجينيه للبروتين الجاذب الكيميائى للخلايا وحيدة النواة، ومستقبل الكيموكين. ومستوى البروتين الجاذب الكيميائى بالدم فى مرض بهجت : دراسة مقارنة

مرض بهجت هو مرض مناعى مزمن يتميز بنوبات متكررة من الالتهابات التى تصيب أجزاء مختلفة من الجسم مثل تقرحات بالفم والتهابات متكررة بالعين، إلى الان لا يوجد سبب واضح للإصابة بمرض بهجت.

هذه الدراسة تهدف إلى معرفة المزيد عن أسباب المرض. تم ادراج ٣٠ مريض مصاب بمرض بهجت فضلاً عن ٣٠ من الأصحاء كمجموعة ضابطة فى هذه الدراسة، وتعرض الجميع لأخذ التاريخ المرضى والفحص السريرى والفحوصات المعملية الروتينية وقياس تعدد الأشكال الجينية فى البروتين الجاذب الكيميائى-١ للخلايا وحيدة النواة والتعدد الجينى لمستقبلات الكيموكين فضلاً عن مستوى البروتين فى الدم.

وأوضحت النتائج ارتفاع ملحوظ لمستوى الجاذب الكيميائى للخلايا وحيدة النواة فى الدم فى المرضى مقارنة بالمجموعة الضابطة بالإضافة لارتفاعه فى الأشخاص الذين يعانون من تعدد الأشكال الجينية فى البروتين الجاذب الكيميائى-١ للخلايا وحيدة النواة ومستقبل الكيموكين، وبناء على ذلك فإن وجود أدوية مضادة البروتين الجاذب الكيميائى للخلايا وحيدة العلاج قد يوفر وسيلة لعلاج مرض بهجت فى المستقبل.